Publications

REiNS Publications

Research findings and recommendations from the REINS working groups have been published in 3 supplemental issues to the journal *Neurology*, one issue of the journal *Clinical Trials*, and across other venues.

Click these links to access the full journal issues:

Neurology. 2013; 81 (21 Suppl 1)

Neurology. 2016; 87 (7 Suppl 1)

Neurology. 2021; 97 (7 Suppl 1)

Clinical Trials. 2024; 21 (1)

Below is a list of the articles published in these supplements organized by topic. Click each topic to jump to the articles:

NF1—Neurofibromatosis type 1

NF2—*NF2*-related schwannomatosis (formerly called neurofibromatosis type 2)

SWN—*SMARCB1*-related schwannomatosis, *LZTR1*-related schwannomatosis, 22q-related schwannomatosis, schwannomatosis-NOS (not otherwise specified), or schwannomatosis-NEC (not elsewhere classified)

REiNS Publications Listed by Topic:

About REiNS

Achieving consensus for clinical trials: The REiNS International Collaboration

Plotkin SR, Blakeley JO, Dombi E, Fisher MJ, Hanemann CO, Walsh KS, Wolters PL, Widemann BC. Achieving consensus for clinical trials: the REiNS International Collaboration. *Neurology*. 2013;81(21 Suppl 1):S1-S5. doi:10.1212/01.wnl.0000435743.49414.b6. PMID: 24249801.

Most early NF clinical trials used study designs similar to those used in cancer trials; however, because of differences in disease symptoms and tumor growth compared to solid cancers, there is a need for new designs that are better suited to NF. The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration was established in 2011 to reach agreement within the NF community about the design of future trials, with an emphasis on measures of response to treatment, also known as endpoints. This paper is an introduction to the first REiNS supplement published in 2013, which includes the first series of recommendations by the REiNS Collaboration.

Full Text (Web) **Full Text (PDF)** **NF1** ***NF2*-SWN** **SWN**

Conclusions and future directions for the REiNS International Collaboration

Widemann BC, Blakeley JO, Dombi E, Fisher MJ, Hanemann CO, Walsh KS, Wolters PL, Plotkin SR. Conclusions and future directions for the REiNS International Collaboration. *Neurology*. 2013;81(21 Suppl 1):S41-S44. doi:10.1212/01.wnl.0000435748.79908.c5. PMID: 24249805.

This paper is the conclusion to the first REiNS supplement published in 2013. It summarizes the first series of recommendations, addresses how they should be used in the context of NF clinical trials, and discusses future recommendations under development.

Full Text (Web) Full Text (PDF) **NF1** ***NF2*-SWN** **SWN**

Consensus for NF clinical trials: Recommendations of the REiNS collaboration (Supplement II)

Widemann BC, Plotkin SR. Consensus for NF clinical trials: Recommendations of the REiNS collaboration (Supplement II). *Neurology*. 2016;87(7 Supplement 1):S1-S3. doi:10.1212/WNL.0000000000002930.

This paper is an introduction to the second REiNS supplement published in 2016, which provides an update on clinical trials that have used the recommended measures from the first supplement. It also summarizes new recommendations for additional measures of response to treatment (endpoints) included in the rest of the supplement.

Full Text (Web) Full Text (PDF) **NF1** ***NF2*-SWN** **SWN**

Neurofibromatosis Clinical Trials—REiNS Collaboration 2020 Recommendations: Looking Back and Moving Ahead

Gross AM, Plotkin SR, Widemann BC, on behalf of the REiNS International Collaboration. Neurofibromatosis Clinical Trials—REiNS Collaboration 2020 Recommendations: Looking Back and Moving Ahead. *Neurology.* 2021;97(7 Supplement 1):S1-S3. doi:10.1212/WNL.0000000000012429. PMID: 34230201.

This introduction to the third REiNS supplement published in 2021 provides a table of past REiNS recommendations and introduces the topics covered within the rest of the supplement. It also includes reflections on the use of REiNS Criteria in the FDA approval of the first medication for NF1 (selumetinib) and what we have learned from that experience.

Full Text (Web) Full Text (PDF) **NF1** ***NF2*-SWN** **SWN**

Advancing neurofibromatosis and schwannomatosis clinical trial design: Consensus recommendations from the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration

Merker VL, Gross AM, Widemann BC, Plotkin SR. Advancing neurofibromatosis and schwannomatosis clinical trial design: Consensus recommendations from the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration. *Clinical Trials*. 2024;21(1):3-5. doi:10.1177/17407745231201345. PMID: 37776044.

This paper is the introduction to the fourth REiNS supplement published in 2024. It provides an overview of the papers in the supplement, and provides updates on the ongoing work of REiNS, including the addition of a new gene-targeted therapy working group.

Full Text (Web) Full Text (PDF) **NF1** ***NF2*-SWN** **SWN**

Biomarkers

Current status and recommendations for biomarkers and biobanking in neurofibromatosis

Hanemann CO, Blakeley JO, Nunes FP, Robertson K, Stemmer-Rachamimov A, Mautner V, Kurtz A, Ferguson M, Widemann BC, Evans DG, Ferner R, Carroll SL, Korf B, Wolkenstein P, Knight P, Plotkin SR, on behalf of the REiNS International Collaboration. Current status and recommendations for biomarkers and biobanking in neurofibromatosis. *Neurology*. 2016;87(7 Suppl 1):S40-S48. doi:10.1212/WNL.0000000000002932. PMID: 27527649.

This paper describes the existing biomarkers in NF, recommends standard operating procedures (SOPs) for the collection of biological samples in NF, and recommends the clinical information that should accompany all samples.

Full Text (Web) Full Text (PDF) **NF1** ***NF2*-SWN** **SWN**

Genotype-Phenotype Correlations in Neurofibromatosis and Their Potential Clinical Use

Bettegowda C, Upadhayaya M, Evans DG, Kim A, Mathios D, Hanemann CO, on behalf of the REiNS International Collaboration. Genotype-Phenotype Correlations in Neurofibromatosis and Their Potential Clinical Use. *Neurology*. 2021;97(7 Suppl 1):S91-S98. doi:10.1212/WNL.0000000000012436. PMID: 34230207.

The goal of this paper was to determine how genotype-phenotype correlations (the relationship between a person's genetic mutation and symptoms) can be used in clinical trials and clinical consultations for NF1 and NF2-*SWN. For NF1, more information is needed to determine how this should impact clinical care and clinical trials. For* NF2-*SWN, REINS recommends grouping patients by genetic severity score for clinical trials.*

Full Text (Web) **Full Text (PDF)** **NF1** ***NF2*-SWN**

Recommendations for the collection and annotation of biosamples for analysis of biomarkers in neurofibromatosis and schwannomatosis clinical trials.

Sundby RT, Rhodes SD, Komlodi-Pasztor E, Sarnoff H, Grasso V, Upadhyaya M, Kim A, Evans DG, Blakeley JO, Hanemann CO, Bettegowda C. Recommendations for the collection and annotation of biosamples for analysis of biomarkers in neurofibromatosis and schwannomatosis clinical trials. *Clini cal Trials*. 2024;21(1):40-50. doi:10.1177/17407745231203330. PMID: 37904489.

Biomarkers (from blood, saliva, urine, tumor samples, etc.) may help in the early diagnosis of some NF/SWN complications and in measuring responses to treatment. The goal of this paper is to provide updated guidance regarding the inclusion of biomarker endpoints in NF/SWN clinical trials. It also recommends an updated standardized approach for collecting and reporting data to ensure that data can be compared across studies.

Full Text (Web) **Full Text (PDF)** **NF1** ***NF2*-SWN** **SWN**

Cutaneous Neurofibromas

Perspective of Adults With Neurofibromatosis 1 and Cutaneous Neurofibromas: Implications for Clinical Trials

Cannon A, Pichard DC, Wolters PL, Adsit S, Erickson G, Lessing AJ, Li P, Narmore W, Röhl C, Rosser T, Widemann BC, Blakeley JO, Plotkin SR, on behalf of the REiNS International Collaboration. Perspective of Adults With Neurofibromatosis 1 and Cutaneous Neurofibromas: Implications for Clinical Trials. *Neurology*. 2021;97(7 Suppl 1):S15-S24. doi:10.1212/WNL.0000000000012425. PMID: 34230202.

This paper presents a survey exploring the experiences of NF1 adults with cutaneous neurofibromas, taking into account their location, size, color, pain, and itchiness. The survey also asked patients' opinions about treatment options, what would be considered a successful treatment, and what side effects would be acceptable.

Full Text (Web) **Full Text (PDF)** **NF1**

Measuring the Effect of Cutaneous Neurofibromas on Quality of Life in Neurofibromatosis Type 1

Maguiness S, Berman Y, Rubin N, Dodds M, Plotkin SR, Wong C, Moertel C, on behalf of the REiNS International Collaboration. Measuring the Effect of Cutaneous Neurofibromas on Quality of Life in Neurofibromatosis Type 1. *Neurology*. 2021;97(7 Suppl 1):S25-S31. doi:10.1212/WNL.0000000000012427. PMID: 34230204.

This paper explores the use of the Skindex, a general dermatology questionnaire, to assess the effects of skin conditions on people with NF1 in the US and Australia. The study showed that NF1-related skin issues may negatively impact physical, emotional, and functional aspects of quality of life (QOL), with features such as the number of cutaneous neurofibromas (cNFs), female sex, and the presence of facial cNFs being most associated with lower scores. It also highlighted the need to design more specific NF1 skin-related QOL measures.

Full Text (Web) **Full Text (PDF)** **NF1**

Validating Techniques for Measurement of Cutaneous Neurofibromas: Recommendations for Clinical Trials

Thalheimer RD, Merker VL, Ly KI, Champlain A, Sawaya J, Askenazi NL, Herr HP, Da JLW, Jordan JT, Muzikansky A, Pearce EM, Sakamoto FH, Blakeley JO, Anderson RR, Plotkin SR, on behalf of the REiNS International Collaboration. Validating Techniques for Measurement of Cutaneous Neurofibromas: Recommendations for Clinical Trials. *Neurology*. 2021;97(7 Suppl 1):S32-S41. doi:10.1212/WNL.0000000000012428. PMID: 34230197.

Researchers evaluated three techniques to measure cutaneous neurofibromas (cNFs): high-frequency ultrasound, 3D photography, and digital calipers. Within each technique, the measurements were consistent with repeated testing. Considerations for choosing which method to use for clinical trials include: cNF size, cNF type, cost, and time to perform measurements.

Full Text (Web) **Full Text (PDF)** **NF1**

Status and Recommendations for Incorporating Biomarkers for Cutaneous Neurofibromas Into Clinical Research

Wallis D, Stemmer-Rachamimov A, Adsit S, Korf B, Pichard D, Blakeley J, Sarin KY, on behalf of the REiNS International Collaboration. Status and Recommendations for Incorporating Biomarkers for Cutaneous Neurofibromas Into Clinical Research. *Neurology*. 2021;97(7 Suppl 1):S42-S49. doi:10.1212/WNL.0000000000012426. PMID: 34230199.

REiNS reviewed existing data on cutaneous neurofibroma (cNF) biomarkers to assess their usefulness in clinical trials. Their investigation concluded that there is a lack of validated cNF biomarkers and made recommendations for future research.

Full Text (Web) **Full Text (PDF)** **NF1**

Perspectives of adolescents with neurofibromatosis 1 and cutaneous neurofibromas: Implications for clinical trials

Cannon A, Sarin KY, Petersen AK, Pichard DC, Wolters PL, Erickson G, Lessing AJ, Li P, Röhl C, Rosser T, Widemann BC, Blakeley JO, Plotkin SR. Perspectives of adolescents with neurofibromatosis 1 and cutaneous neurofibromas: Implications for clinical trials. *Clinical Trials*. 2024;21(1):67-72. doi: 10.1177/17407745231178839. PMID: 37269078.

This paper presents the results of a survey of adolescents with NF1 and their caregivers regarding how their cutaneous neurofibromas (cNFs) affect them and their preferences for treatment. Adolescents had several negative feelings about their cNFs and worried most about them getting worse over time. Bot h adolescents and their caregivers would be interested in longer-term experimental treatments for cNFs, as long as the side effects were minimal.

Full Text (Web) **Full Text (PDF)** **NF1**

A core outcome domain set to assess cutaneous neurofibromas related to neurofibromatosis type 1 in clinical trials

Fertitta L, Bergqvist C, Sarin KY, Plotkin SR, Moertel C, Petersen AK, Cannon A, Berman Y, Pichard DC, Röhl C, Lessing A, Brizion B, Peiffer B, Ravaud P, Tran VT, Armand ML, Moryousef S, Ferkal S, Jannic A, Ezzedine K, Wolkenstein P; Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) international collaboration. A core outcome domain set to assess cutaneous neurofibromas related to neurofibromatosis type 1 in clinical trials. *Br J Dermatol*. 2024 Jan 23;190(2):216-225. doi: 10.1093/bjd/ljad397. PMID: 37877514.

Based on input from more than 200 NF1 patients, family members, clinicians, and researchers from 21 different countries, the 19 most important outcomes to measure in cNF clinical trials were identified. These fell into four main categories: clinical assessment, daily life impact, patient satisfaction, and perception of health. The next step will be to determine the best way to consistently measure and compare these outcomes in clinical trials.

Abstract **Lay Summary** **Author Video** **NF1**

Functional Outcomes

Functional outcome measures for NF1-associated optic pathway glioma clinical trials

Fisher MJ, Avery RA, Allen JC, Ardern-Holmes SL, Bilaniuk LT, Ferner RE, Gutmann DH, Listernick R, Martin S, Ullrich NJ, Liu GT, for the REiNS International Collaboration. Functional outcome measures for NF1-associated optic pathway glioma clinical trials. *Neurology*. 2013;81(21 Suppl 1):S15-S24. doi:10.1212/01.wnl.0000435745.95155.b8. PMID: 24249802.

For patients with NF1-associated optic pathway gliomas (OPG), the main goal of treatment is maintaining or improving vision. Therefore, the success of a treatment for OPG should be primarily based on measures of vision rather than changes in tumor size. REiNS recommends visual acuity, which is how well someone can see, as the best measure (or primary endpoint) for use in clinical trials in children with OPG. This paper also recommends the best methods for measuring visual acuity in children and reviews the suitability of other measures of vision as secondary endpoints for clinical trials.

Full Text (Web) **Full Text (PDF)** **NF1**

Hearing and facial function outcomes for neurofibromatosis 2 clinical trials

Plotkin SR, Ardern-Holmes SL, Barker FG, Blakeley JO, Evans DG, Ferner RE, Hadlock TA, Halpin C, for the REiNS International Collaboration. Hearing and facial function outcomes for neurofibromatosis 2 clinical trials. *Neurology*. 2013;81(21 Suppl 1):S25-S32. doi:10.1212/01.wnl.0000435746.02780.f6. PMID: 24249803.

Hearing loss and facial weakness are important functional outcomes for NF2-*SWN clinical trials; however, there was a lack of agreement concerning how to measure responses to treatment. REiNS recommends the use of maximum word recognition score as a primary hearing outcome measure. The group also recommends the scaled measurement of improvement in lip excursion (SMILE) system as a primary outcome measure for studies of facial function.*

Full Text (Web) **Full Text (PDF)** ***NF2*-SWN**

Sleep and pulmonary outcomes for clinical trials of airway plexiform neurofibromas in NF1

Plotkin SR, Davis SD, Robertson KA, Akshintala S, Allen J, Fisher MJ, Blakeley JO, Widemann BC, Ferner RE, Marcus CL, for the REiNS International Collaboration. Sleep and pulmonary outcomes for clinical trials of airway plexiform neurofibromas in NF1. *Neurology*. 2016;87(7 Suppl 1):S13-S20. doi: 10.1212/WNL.0000000000002933. PMID: 27527645.

Airway function and sleep are important functional outcome measures for people with NF1-related airway plexiform neurofibromas. REiNS recommends using the Apnea Hypopnea Index (AHI) for measuring sleep quality and using either airway resistance calculations or forced expiratory volume for measuring airway function in NF1 clinical trials.

Full Text (Web) **Full Text (PDF)** **NF1**

Reliability of Handheld Dynamometry to Measure Focal Muscle Weakness in Neurofibromatosis Types 1 and 2

Akshintala S, Khalil N, Yohay K, Muzikansky A, Allen J, Yaffe A, Gross AM, Fisher MJ, Blakeley JO, Oberlander B, Pudel M, Engelson C, Obletz J, Mitchell C, Widemann BC, Stevenson DA, Plotkin SR, on behalf of the REiNS International Collaboration. Reliability of Handheld Dynamometry to Measure Focal Muscle Weakness in Neurofibromatosis Types 1 and 2. *Neurology*. 2021;97(7 Suppl 1):S99-S110. doi:10.1212/WNL.0000000000012439. PMID: 34230196.

Muscle weakness may be seen in many patients with NF1 and NF2-*SWN, either due to nerve sheath tumors or other reasons. A handheld dynamometer (HHD) is a device that allows for the objective measurement of muscle strength. The study found that when used by a trained examiner following a standard protocol, HHD is a reliable device that can be used in future clinical trials for patients with NF1 and* NF2-*SWN.*

Full Text (Web) **Full Text (PDF)** **NF1** ***NF2*-SWN**

Potential endpoints for assessment of bone health in persons with neurofibromatosis type 1

Gross AM, Plotkin SR, Watts NB, Fisher MJ, Klesse LJ, Lessing AJ, McManus ML, Larson AN, Oberlander B, Rios JJ, Sarnoff H, Simpson BN, Ullrich NJ, Stevenson DA. Potential endpoints for assessment of bone health in persons with neurofibromatosis type 1. *Clinical Trials*. 2024;21(1):29-39. doi:10.1177/17407745231201338. PMID: 37772407.

Bone-related problems, such as abnormal spinal curvature (scoliosis), low bone mineral density, and abnormal bone formation, can cause significant challenges for people with NF1. However, there is still much we do not know about how these problems develop and change over time. This review summarizes the methods available for measuring bone health in people with NF1 and reviews the strengths and weaknesses of each for use in a possible future NF1 bone natural history study.

Full Text (Web) **Full Text (PDF)** **NF1**

Gene-Targeted Therapy

Gene-targeted therapy for neurofibromatosis and schwannomatosis: The path to clinical trials

Staedtke V, Anstett K, Bedwell D, Giovannini M, Keeling K, Kesterson R, Kim Y, Korf B, Leier A, McManus ML, Sarnoff H, Vitte J, Walker JA, Plotkin SR, Wallis D. Gene-targeted therapy for neurofibromatosis and schwannomatosis: The path to clinical trials. *Clinical Trials*. 2024;21(1):51-66. doi:10.1177/17407745231207970. PMID: 37937606.

Although gene-targeted therapies are becoming available to treat many rare diseases, NF/SWN are not currently among them. This paper discusses the state of the science of gene-targeted therapy as well as how the NF/SWN community should prepare for future clinical trials.

Full Text (Web) **Full Text (PDF)** **NF1** ***NF2*-SWN** **SWN**

Imaging

Recommendations for imaging tumor response in neurofibromatosis clinical trials

Dombi E, Ardern-Holmes SL, Babovic-Vuksanovic D, Barker FG, Connor S, Evans DG, Fisher MJ, Goutagny S, Harris GJ, Jaramillo D, Karajannis MA, Korf BR, Mautner V, Plotkin SR, Poussaint TY, Robertson K, Shih CS, Widemann BC, for the REiNS International Collaboration. Recommendations for imaging tumor response in neurofibromatosis clinical trials. *Neurology*. 2013;81(21 Suppl 1):S33-S40. doi:10.1212/01.wnl.0000435744.57038.af. PMID: 28029918.

Standardized criteria commonly used in clinical trials for cancers are not practical to assess benign NF-related tumors, such as plexiform neurofibromas or vestibular schwannomas. These tumors can have complex shapes and grow relatively slowly, therefore more sensitive methods are needed to detect change. REiNS recommends using 3D volume measurements from MRI to define response in clinical trials. This paper also specifies how these MRIs should be obtained and proposes criteria for assessing tumor growth or shrinkage over time.

Full Text (Web) **Full Text (PDF)** **NF1** ***NF2*-SWN** **SWN**

Current whole-body MRI applications in the neurofibromatosis: NF1, NF2, and schwannomatosis

Ahlawat S, Fayad LM, Khan MS, Bredella MA, Harris GJ, Evans DG, Farschtschi S, Jacobs MA, Chhabra A, Salamon JM, Wenzel R, Mautner VF, Dombi E, Cai W, Plotkin SR, Blakeley JO. Current whole-body MRI applications in the neurofibromatoses: NF1, NF2, and schwannomatosis. *Neurology*. 2016;87 (7 Suppl 1):S31-S39. doi:10.1212/WNL.0000000000002929. PMID: 27527647.

Whole-body MRI (WB-MRI) can identify and measure internal tumors in people with neurofibromatosis and schwannomatosis (NF/SWN). REiNS reviewed the literature to assess the best method of performing and interpreting WB-MRI so it can be used as a tool in NF/SWN clinical trials. Although there are many ways of performing WB-MRI, the REiNS group agreed that a specific technique called STIR should be included as a core sequence to allow for consistent tumor measurement.

Full Text (Web) **Full Text (PDF)** **NF1** ***NF2*-SWN** **SWN**

Imaging Evaluation of Plexiform Neurofibromas in Neurofibromatosis Type 1: A Survey-Based Assessment

Ahlawat S, Ly KI, Fayad LM, Fisher MJ, Lessing AJ, Berg DJ, Salamon JM, Mautner VF, Babovic-Vuksanovic D, Dombi E, Harris G, Plotkin SR, Blakeley J, on behalf of the REiNS International Collaboration. Imaging Evaluation of Plexiform Neurofibromas in Neurofibromatosis Type 1: A Survey-Based Assessment. *Neurology*. 2021;97(7 Suppl 1):S111-S119. doi:10.1212/WNL.0000000000012437. PMID: 34230200.

REiNS surveyed NF1 clinicians about their use of imaging to identify and monitor plexiform neurofibromas (PNs) in patients with NF1. Regional (localized) MRI was consistently used for patients with known PN or symptoms of a PN. However, there was a wide variety of approaches to screening asymptomatic patients with no known PN. This supports the need to establish guidelines on when and how to image NF1 patients to diagnose and monitor PNs.

Full Text (Web) **Full Text (PDF)** **NF1**

Neurocognitive Outcomes

Neurocognitive outcomes in neurofibromatosis clinical trials: Recommendations for the domain of attention

Walsh KS, Janusz J, Wolters PL, Martin S, Klein-Tasman BP, Toledo-Tamula MA, Thompson HL, Payne JM, Hardy KK, de Blank P, Semerjian C, Gray LS, Solomon SE, Ullrich N, for the REiNS International Collaboration. Neurocognitive outcomes in neurofibromatosis clinical trials: Recommendations for the domain of attention. *Neurology*. 2016;87(7 Suppl 1):S21-S30. doi:10.1212/WNL.0000000000002928. PMID: 27527646.

The goal of this paper is to identify standardized and specific cognitive assessment tools for use in measuring attention in school-aged children with NF1. The Digit Span subtest from the Wechsler scales was the recommended performance measure of attention. The Conners scales were the recommended measure of behavioral problems associated with attention.

Full Text (Web) **Full Text (PDF)** **NF1**

Recommendations for Social Skills End Points for Clinical Trials in Neurofibromatosis Type 1

Janusz JA, Klein-Tasman BP, Payne JM, Wolters PL, Thompson HL, Martin S, de Blank P, Ullrich N, Del Castillo A, Hussey M, Hardy KK, Haebich K, Rosser T, Toledo-Tamula MA, Walsh KS, on behalf of the REiNS International Collaboration. Recommendations for Social Skills End Points for Clinical Trials in Neurofibromatosis Type 1. *Neurology*. 2021;97(7 Suppl 1):S73-S80. doi:10.1212/WNL.0000000000012422. PMID: 34230205.

Many children and adolescents with NF1 have difficulty with various aspects of social functioning. REiNS reviewed and evaluated current literature for outcome measures of social skills in people ages 6-18. The Social Skills Improvement System-Rating Scales (SSIS-RS) was recommended for clinical trials focusing on broad social functioning, while the Social Responsiveness Scale, Second Edition (SRS-2), was recommended for studies on problematic social behaviors associated with autism spectrum disorder.

Full Text (Web) **Full Text (PDF)** **NF1**

Recommendations for Measurement of Attention Outcomes in Preschoolers With Neurofibromatosis

Klein-Tasman BP, Lee K, Thompson HL, Janusz J, Payne JM, Pardej S, de Blank P, Kennedy T, Janke KM, Castillo AD, Walsh KS, on behalf of the REiNS International Collaboration. Recommendations for Measurement of Attention Outcomes in Preschoolers With Neurofibromatosis. *Neurology*. 2021; 97(7 Suppl 1):S81-S90. doi:10.1212/WNL.0000000000012423. PMID: 34230206.

This paper is a review of current performance-based and observer-rated measures of attention in preschool-aged children with NF1. In contrast to the recommendations for school-aged children, the Attention Deficit Hyperactivity Disorder Rating Scale-Preschool (ADHD-RS-P) was recommended for preschoolers; additional measures were recommended as secondary outcomes. It also provides practical guidelines for clinical trials targeting this age group.

Full Text (Web) **Full Text (PDF)** **NF1**

Perspectives of adults with neurofibromatosis regarding the design of psychosocial trials: Results from an anonymous online survey

Wolters PL, Ghriwati NA, Baker M, Martin S, Berg D, Erickson G, Franklin B, Merker VL, Oberlander B, Reeve S, Röhl C, Rosser T, Vranceanu AM. Perspectives of adults with neurofibromatosis regarding the design of psychosocial trials: Results from an anonymous online survey. *Clinical Trials*. 2024; 21(1):73-84. doi:10.1177/17407745231209224. PMID: 37962219.

REiNS surveyed adults with NF/SWN about their psychosocial well-being and preferences for interventions. Many indicated that NF/SWN affected their well-being, including social, emotional, and learning difficulties during childhood, but that they often did not receive assistance. Most would be willing to participate in a clinical trial targeted to reduce anxiety, develop a healthier lifestyle, or cope with stress. The survey results emphasize the need for meaningful behavioral interventions that are consistent with concerns and preferences of adults with NF/SWN.

Full Text (Web) **Full Text (PDF)** **NF1** ***NF2*-SWN** **SWN**

Patient Engagement

Enhancing Neurofibromatosis Clinical Trial Outcome Measures Through Patient Engagement: Lessons From REiNS

Merker VL, Lessing AJ, Moss I, Hussey M, Oberlander B, Rose T, Thalheimer R, Wirtanen T, Wolters PL, Gross AM, Plotkin SR, on behalf of the REiNS Int ernational Collaboration. Enhancing Neurofibromatosis Clinical Trial Outcome Measures Through Patient Engagement: Lessons From REiNS. *Neurology*. 2021;97(7 Suppl 1):S4-S14; doi:10.1212/WNL.0000000000012430

> *The REINS patient representative program began in fall 2017 to include patients with NF1, NF2, and schwannomatosis and their family members in clinical trial design. This paper shows the positive impact patient representatives had on REiNS, including how they worked with researchers to develop better clinical trial outcome measures. It also discusses what made it easier or harder for patient representatives to participate in REiNS.*

Full Text (Web) **Full Text (PDF)** **NF1** **NF2** **SWN**

Patient-Reported Outcomes

Patient-reported outcomes in neurofibromatosis and schwannomatosis clinical trials

Wolters PL, Martin S, Merker VL, Gardner KL, Hingtgen CM, Tonsgard JH, Schorry EK, Baldwin A, for the REiNS International Collaboration. Patient-reported outcomes in neurofibromatosis and schwannomatosis clinical trials. *Neurology*. 2013;81(21 Suppl 1):S6-S14. doi:10.1212/01.wnl.0000435747.02780.bf. PMID: 24249806.

REiNS developed a systematic process to rate existing patient-reported outcomes for use in NF clinical trials. Using this process, they reviewed measures of pain intensity and recommended using the Numerical Rating Scale (NRS-11), a 0-10 pain scale.

Full Text (Web) **Full Text (PDF)** **NF1** ***NF2*-SWN** **SWN**

Patient-reported outcomes of pain and physical functioning in neurofibromatosis clinical trials

Wolters PL, Martin S, Merker VL, Tonsgard JH, Solomon SE, Baldwin A, Bergner AL, Walsh K, Thompson HL, Gardner KL, Hingtgen CM, Schorry E, Dudley WN, Franklin B, for the REiNS International Collaboration. Patient-reported outcomes of pain and physical functioning in neurofibromatosis clinical trials. *Neurology*. 2016;87(7 Suppl 1):S4-S12. doi:10.1212/WNL.0000000000002927. PMID: 27527648.

Measuring whether new treatments impact how people feel and function is important for regulatory approval. REiNS reviewed existing measures of pain interference to determine which ones were best suited for NF clinical trials. The group recommended the Pain Interference Index (PII) for children /adolescents and the Patient-Reported Outcomes Measurement Information System (PROMIS) Pain Interference Scale for adults. The group also reviewed measures of physical functioning and recommended the PROMIS Physical Functioning Scale for all ages.

Full Text (Web) **Full Text (PDF)** **NF1** ***NF2*-SWN** **SWN**

Patient Report of Hearing in Neurofibromatosis Type 2: Recommendations for Clinical Trials

Thompson HL, Blanton A, Franklin B, Merker VL, Franck KH, Welling DB, on behalf of the REiNS International Collaboration. Patient Report of Hearing in Neurofibromatosis Type 2: Recommendations for Clinical Trials. *Neurology*. 2021;97(7 Suppl 1):S64-S72. doi:10.1212/WNL.0000000000012424. PMID: 34230203.

Changes in hearing are typically measured with audiology testing in NF2-*SWN clinical trials, but there is also a need to understand if people with* NF2-*SWN personally feel their hearing and quality of life (QOL) has improved due to experimental treatments. REiNS reviewed existing patient-reported measures of hearing function and hearing-related QOL, and recommended the Self-Assessment of Communication (SAC) for use in future* NF2-*SWN clinical trials.*

Full Text (Web) **Full Text (PDF)** ***NF2*-SWN**

Current Recommendations for Patient-Reported Outcome Measures Assessing Domains of Quality of Life in Neurofibromatosis Clinical Trials

Wolters PL, Vranceanu AM, Thompson HL, Martin S, Merker VL, Baldwin A, Barnett C, Koetsier KS, Hingtgen CM, Funes CJ, Tonsgard JH, Schorry EK, Allen T, Smith T, Franklin B, Reeve S, on behalf of the REiNS International Collaboration. Current Recommendations for Patient-Reported Outcome Measures Assessing Domains of Quality of Life in Neurofibromatosis Clinical Trials. *Neurology*. 2021;97(7 Suppl 1):S50-S63. doi:10.1212/WNL.0000000000012421. PMID: 4230198.

This paper reviews existing patient-reported measures of quality of life for use in NF clinical trials. The group recommended several generic measures of quality of life (QOL) depending on the ages of the patients and purpose of the trial. For disease-specific measures of quality of life, the group recommended the Pediatric Quality of Life Inventory (PedsQL) NF1 module for NF1 trials and the NF2-*SWN Impact on Quality of Life (NFTI-QOL) for* NF2-*SWN trials.*

Full Text (Web) **Full Text (PDF)** **NF1** ***NF2*-SWN** **SWN**

Patient-reported measures of tinnitus for individuals with neurofibromatosis type 2-related schwannomatosis: Recommendations for clinical trials

Thompson HL, Grabowski J, Franklin B, Koetsier KS, Welling DB. Patient-reported measures of tinnitus for individuals with neurofibromatosis type 2-related schwannomatosis: Recommendations for clinical trials. *Clinical Trials*. 2024 Feb;21(1):18-28. doi:10.1177/17407745231217279. PMID: 38321701.

Tinnitus, which is the perception of sound that no one else hears, like ringing in the ears, is common in people with NF2-*SWN. While it is known to have a negative impact on quality of life of individuals from the general population, the impact on those with* NF2-*SWN is unknown. REiNS reviewed existing patient-reported measures of tinnitus, and recommended the Tinnitus Functional Index for use in* NF2-*SWN clinical trials.*

Full Text (Web) **Full Text (PDF)** **NF1**

Recommendations for assessing appearance concerns related to plexiform and cutaneous neurofibromas in neurofibromatosis 1 clinical trials

Merker VL, Thompson HL, Wolters PL, Buono FD, Hingtgen CM, Rosser T, Barton B, Barnett C, Smith T, Haberkamp D, McManus ML, Baldwin A, Moss IP, Röhl C, Martin S. Recommendations for assessing appearance concerns related to plexiform and cutaneous neurofibromas in neurofibromatosis 1 clinical trials. *Clinical Trials*. 2024;21(1):6-17. doi:10.1177/17407745231205577. PMID: 38140900.

New treatments for plexiform neurofibromas or cutaneous neurofibromas may improve the way people look, but there is no standardized way to measure how people with NF1 feel about their appearance during clinical trials. REINS reviewed existing patient-reported measures of appearance and recommended the FACE-Q Craniofacial Module Appearance Distress subscale for use in future NF1 clinical trials. While this measure was originally designed for individuals with facial disorders, REiNS recommends using this scale for appearance issues anywhere across the body.

Full Text (Web) **Full Text (PDF)** **NF1**